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Apheresis in the Treatment of Systemic Lupus Erythematosus (SLE)

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NATIONAL CENTER FOR HEALTH SERVICES RESEARCH AND HEALTH CARE TECHNOLOGY ASSESSMENT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOREWORD

The Office of Health Technology Assessment (OHTA) evaluates the safety and effectiveness of new or unestablished medical technologies that are being considered for coverage under Medicare. These assessments are done at the request of DHHS' Health Care Financing Administration (HCFA), which uses them in support of medicare policy and decisionmaking.

Questions about Medicare coverage for certain health care technologies are directed to HCFA by such interested parties as insurers, manufacturers, Medicare contractors, and practitioners. Those of a medical, scientific, or technical nature are formally referred to OHTA for assessment.

OHTA's assessment activities include a comprehensive review of the medical literature and emphasize broad and open participation from within and outside the Federal Government. A range of expert advice is obtained by widely publicizing plans for input from Federal agencies, medical specialty societies, insurers, and manufacturers. The involvement of these experts helps assure the experience and varying viewpoints needed to round out the data derived from individual scientific studies and medical specialty analyses.

After OHTA receives information from experts and the scientific literature, the results are incorporated and synthesized into an assessment report. The Health Technology Assessment Reports form the basis for OHTA's communication to HCFA and are widely disseminated.

OHTA is part of the National Center for Health Services Research and Health Care Technology Assessment, Office of the Assistant Secretary for Health, Public Health Service, DHHS.

Enrique D. Carter, M.D.
Director Office of Health
Technology Assessment

John E. Marshall, Ph.D.
Director, National Center for
Health Services Research and Health
Care Technology Assessment

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ASSESSMENT OF

APHERESIS IN THE TREATMENT OF

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

1985

Apheresis is a technique which permits the selective removal of plasma or other blood components from the circulation. The primary use of apheresis has been to collect platelets or leucocytes from normal donors to be transfused into patients deficient in these blood product components. Apheresis has been used therapeutically in the treatment of several diseases such as hyperviscosity and thrombocytosis, in which specific substances can be identified and removed (1). Apheresis has also been used with success in the management of some autoimmune diseases such as Goodpasture's syndrome. It has been investigated in other diseases such as Guillain-Barre Syndrome, myasthenia gravis, lupus erythematosus, dermatomyositis and chronic relapsing polyneuropathy in which the clinical manifestations are often associated with circulating immune complexes (2). The procedure commonly requires a blood processing machine. The machine pumps anticoagulated venous blood through an extracorporeal circuit into a centrifuge type cell separator (3). More recently, devices using filtration via semipermeable membranes or affinity columns have also been applied to apheresis (4,5). These techniques ideally require identification of the specific plasma constituents to be removed (6). Commercially available cell separators used for apheresis utilize either continuous or intermittent flow centrifugation. The continuous flow systems allow constant withdrawal of small volumes of blood from the patient. Blood components are separated and selected fractions reinfused. The desired components are infused into the patient. The intermittent systems require a predetermined amount of blood to be

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withdrawn to fill the centrifuge bowl. This blood is differentially centrifuged and then reinfused into the patient (7). Depending on the device used, plasma, macromolecules and/or formed elements in the blood such as lymphoctyes can also be removed. Blood and appropriate isovolemic and isotonic fluids are then reinfused into the patient. The most commonly used replacement solutions are cystalloids, normal serum albumin, plasma protein fractions and fresh frozen plasma (8). Both albumin and fresh frozen plasma are associated with potential risks for acquiring viral hepatitis or other viral infections such as CMV and AIDS (9).

Apheresis is being performed in various inpatient and outpatient settings including hospitals, dialysis centers, blood banks and physicians' offices (10). Although standardized procedures for apheresis do not exist, the process commonly involves the transfer of 1-1.5 patient plasma volumes. It takes an average of 2-4 hours, and is usually repeated, daily or on alternate days. The frequency of treatment is determined by the type and severity of the disease being treated (11). In 1981 approximately 50,000 apheresis procedures were performed in the United States and more than 3,000 throughout Europe, Japan, and Canada in the treatment of more than 50 different diseases of varied etiologies. Apheresis is used most often for diseases that are presumed to be immunologically mediated and that do not respond to other conventional treatments (12).

BACKGROUND

Systemic lupus erythematosus (SLE) is a spontaneously occurring, multisystem, inflammatory connective tissue disease of unknown etiology (13, 14). The disease has an annual incidence of approximately 2/100,000 (15). According to the Lupus Foundation, there are more than 50,000 new cases diagnosed each year and the disease affects more than 500,000 people in the United States.

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SLE usually begins in adolescence. Approximately 90 percent of patients are females. The clinical manifestations of the disease are protean and include inflammation of the skin and the mucosal and serosal surfaces of tissues and organs (16). The most common clinical manifestations of SLE in decreasing order of frequency are; arthritis, fever, rash, pleurisy, nephritis, central nervous system involvement, pneumonia, and heart disease (17). Although SLE affects multiple systems, the lesions that generally determine the course of the disease are found in the kidneys (18). Approximately 40 percent of SLE patients have renal involvement. Nephritis is the major cause of end stage renal failure and other serious morbidity and death (19, 20). The overall 10 year survival of SLE patients is 90 percent, with approximately 5000 deaths per year (21). SLE patients with nephritis have a 5 year survival of 67 percent versus 85-95 percent for those patients without nephritis (14).

Clinically, SLE resembles experimental chronic serum sickness which is mediated by circulating immune complexes, and SLE is regarded as the prototypic immune complex disease in man (16, 18). The hallmark of SLE is the presence of B-lymphocyte hyperactivity as manifested by hypergammaglobulinemia and a myriad of autoantibodies directed against several nuclear and cytoplasmic membrane constituents (22).

Genetic factors appear to play a predisposing role in SLE (13). However, the stimulus for the formation of the various auto-antibodies found in the majority of patients with SLE has not been classified. Both endogenous and environmental factors (hormones, infections, chemical and physical agents) have been suggested as possible sources that trigger autoantibody production and augment the expression of the illness (13,18,23). It is hypothesized that these antibodies, especially in the form of immune complexes (DNA plus anti-DNA antibodies) are of fundamental etiological importance in the pathogenesis of SLE (24, 25). It is widely accepted that the clinical manifestations of

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SLE are mediated through immune complexes which are deposited or formed in the microvasculature of various tissue where they "fix and activate" complement proteins, inducing an acute and chronic inflammatory reaction which produces tissue damage, the so-called classical complement cascade (16,22,26,27,28).

The presence of several different polynucleotide immune complex systems in patients with SLE indicates that the antigen is at least partially of host cellular origin, hence the term "autoimmune disease" applied to SLE (29). Both single and double stranded DNA and anti-DNA antibody comprise the immune complexes thought to be pathogenic (30, 31). Studies of serum antibody titres were inadequate for predicting the type of complexes deposited in tissues and high serum titres are not necessarily correlated with tissue deposition (29).

The treatment of SLE has been empiric, although relatively successful. In 1955 the 5 year survival was 50 percent whereas in 1985 it is 95 percent and the 15 year survival is 80 percent. The vast majority of patients with severe SLE are treated with corticosteroids and/or cytotoxic immunosuppressives which have evolved into the standard treatment for SLE. These treatments, which have never been proven effective in a prospectively randomized clinical trial, are aimed at reducing the patients' antibody response and inflammatory reaction.

The variable and intermittent clinical course of SLE, including spontaneous remissions and relapses and the inadequate methods of assessing disease activity and impending relapses, make the interpretation of the role of any treatment difficult to evaluate (4, 5). A clinical trial involving a large number of patients would be required to test the efficacy of any treatment for this disease (32).

There has been no controlled trial supporting the use of steroids or immunosuppressives in the treatment of SLE. However, in a retro-spective study, the use of steroids was associated with increased survival in patients with severe lupus nephritis (33). In the case of immunosuppressives (Cytoxan, Imuran), a delayed onset of

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nephritis and increased survival was seen in animal models of SLE (33). Conflicting evidence exists for the use of immunosuppressives both for treatment or as maintenance therapy to prevent relapses. The adverse effects of the use of steroids and/or immunosuppressives may also contribute to the morbidity and mortality of the treated disease (34).

RATIONALE

The rationale for the application of apheresis to the treatment of SLE derives from a number of factors. Although the pathogenic mechanisms of SLE are not completely understood, there is considerable evidence implicating circulating factors in the generation of tissue injury and theoretically, removal or dilution of circulating immunopathogens may improve the disease (35). Another potential mechanism of action of apheresis is by improvement of reticuloendothelial system (RES) function. Circulating immune complexes (CIC) are normally cleared by the RES which serves as an important buffer against these potentially inflammatory substances (36). In laboratory animals, blockage or saturation of the RES enhances deposition of CIC in blood vessels. A RES saturated by CIC, in cases of severe SLE, would be unable to clear the serum of high levels of immune complexes exacerbating the disease. Apheresis would effectively "unblock" the RES by removal of excess CIC (37). The "unblocking" of RES function could explain the continued fall in CIC levels after completion of apheresis (38). Apheresis can result in the rapid clearance of antibodies, immune complexes and other mediators of inflammation from the serum (39). However, these effects are transient and followed in experimental animals by a rebound of high levels of these substances via a compensatory increase in antibody synthesis, unless immunosuppression is

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administered. Data supporting this mechanism in man is scant (40). However, patients treated with apheresis without concommitant immunosuppression have a poor outcome, suggesting a possible accelerated clinical deterioration (41).

The syllogism supporting a trial of apheresis in treating SLE is as follows:

A Clinical SLE is a consequence of increased levels of CIC

B Apheresis can effectively lower CIC directly or facilitating their clearance, therefore;

C Apheresis is applied to SLE.

The mechanism of action appears logical: plasma containing noxious substances is removed and replaced by normal plasma constituents and or electrolytes (42, 43).

REVIEW OF THE LITERATURE

The first report of a trial of apheresis in patients with SLE was by Jones et al. in 1976 (44). On the basis of evidence that apheresis had been clinically successful in substantially reducing levels of rhesus isoantibodies in pregnant women, apheresis was carried out in 8 patients with SLE in an attempt to mitigate the acute stages of the disease. In 4 patients in whom there were high levels of CIC, there was marked clinical improvement following the removal of 5-8 litres of plasma weekly. The four other patients in whom there was no evidence of CIC showed no benefit from the treatment.

In a subsequent report, Jones et al. described 6 additional cases (37). In summary, 8 of the 14 patients showed evidence of clinical improvement following apheresis. Three patients showed no response and three others were regarded as unevaluable. Ten patients were receiving steroids at the time of apheresis.

In 1981, in an attempt to isolate the effects of apheresis from that of steroids and cytotoxic drugs, Jones et al. studied 8 patients with SLE who were maintained on constant doses of medication for at least one month prior to apheresis (40). In all cases,

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CIC and anti-DNA antibodies were lowered by apheresis. A rapid rebound to pretreatment levels was seen in 5 of the 8 cases. A prolonged therapeutic response was observed in 3 of the 8 patients in whom apheresis was followed by one month treatment with cyclophosphamide.

In 1977, Moran et al. described two patients with SLE who were treated with apheresis who had moderate, but transient, relief of symptoms following treatments (43).

Lockwood et al., following their success in the treatment of Goodpasture's syndrome by a regimen of apheresis combined with steroids and cytotoxic immunosuppressants, applied this same treatment to 9 patients with fulminating immune-complex nephritis (45). In 5 patients with renal failure, there was rapid improvement in kidney function. One patient exhibited stabilization of an extensive necrotizing glomerulitis. One anuric patient failed to improve and the two additional patients showed improvement 3 and 7 weeks after treatment (which could not be attributed to the therapy). Patients with high levels of CIC appeared to demonstrate the best response to treatment.

In a study of apheresis and splenic function in 10 patients with vasculitis or nephritis, Lockwood et al. included two patients with SLE both of whom demonstrated clinical and laboratory improvement following apheresis (38). One patient had acute vasculitis and nephritis despite prednisone, 40 mg per day, for one month.

Schildermans et al. described a case of severe SLE, uncontrolled by steroids and cyclophosphamide, which exhibited a dramatic response persisting for over 18 months, after three apheresis treatments in one week (28).

Among 11 patients with connective tissue disease treated with apheresis by Dequeker et al., three patients with SLE had both objective and subjective "very good responses" (46). Two of the patients were already taking steroids and

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immunosuppressives for weeks prior to apheresis, without controlling the disease activity. The other patient was given steroids associated with the apheresis. The remissions achieved were sustained during the 14-24 month followup.

Clark et al. studied a well defined subgroup of 8 SLE patients who had diffuse proliferative glomerulonephritis (47). Apheresis, (four litres of plasma replaced by 5 percent albumin) on a monthly basis for an average of 15 months, was associated with an improvement in renal function and a reduction in episodes of disease activity, hospitalizations and requirements for steroid immunosuppressant therapy.

The first report of a randomized controlled clinical trial of apheresis in SLE was also reported by Clark et al. (48). Thirty-nine patients with SLE nephritis were enrolled in a 3 year multicenter study. Twenty patients were treated by apheresis and 19 served as a control receiving steroids $\pm$ cytotoxics. The results of this study indicate a 33 percent better renal function in the treated versus the control patients at a P value of 0.85. In the 30 patients randomized to albumin rather than plasma versus the conventional therapy, a 50 percent better renal function was seen; which is significant at the P value of less than 0.045.

In a study of a heterogenous group of 10 SLE patients who were used as their own controls, Parry et al. reported that a temporary clinical benefit from apheresis was seen in 8 patients (27). Circulating immune complexes were effectively reduced by the treatments but initial levels were unrelated to the clinical responses. This was in contrast to the findings of Jones et al. (37, 40, 42).

In a more recent randomized clinical trial of apheresis in patients with "milder active" SLE, Wei et al., at the National Institutes of Health, evaluated 18 patients who completed the short term study (26). Apheresis produced significant reductions in serum levels of immune globulins and CIC, which subsequently returned to baseline levels 4 weeks after apheresis without evidence of rebound above baseline values. Sixteen of the

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18 patients evaluated had either remained stable or improved. However the frequency and degree of improvement was the same as that seen in the control group, both during the apheresis procedure and one month later. A suggestion of benefit measured at 6 weeks after treatment was not statistically significant.

Hamblin and Smith reported the results of long-term apheresis in 11 patients with SLE (49). The duration of apheresis ranged from 5-75 months and the number of treatments from 18-309. All patients reported subjective improvements and required significantly less steroids during the treatment program.

Seven patients with severe SLE nephritis were treated by Moriconi et al. (50). The patients had failed to respond to high doses of steroids and were treated with apheresis from 14-57 times. Kidney function improved in 4 of 7 patients and remained unchanged in the others. The positive results were obtained despite reduced steroids, and no relapses were observed.

In another report of apheresis used in the treatment of acute lupus nephritis, Vangelista et al. demonstrated a rapid improvement of clinical symptoms in all 11 cases treated (39). However, both steroids and cyclophosphamide were administered to all patients, so that it was impossible to isolate the role of apheresis vis-a-vis the drug therapy.

Habersetzer et al. reported a series of 9 patients with rapidly progressive SLE who had contraindications for conventional therapy (steroids and cytotoxic drugs) and were treated with apheresis (35). Five patients improved, two patients progressed to end-stage renal failure, and two died as a result of complications of advanced SLE.

Schena et al. reported on their experience with short-term apheresis in 8 patients who did not respond to conventional therapy (51). Apheresis was administered for periods ranging from 1-8 months for a total of 6-27 sessions and conventional therapy was continued in these patients. All patients showed an improvement in their renal functions

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as demonstrated by a reduction in serum creatinine and a rise in creatinine clearance. Again, the contribution of the apheresis in these patients is difficult to assess in view of the continued drug therapy and the variability of the clinical course of SLE.

Although apheresis is not risk free, the widespread use of the procedure in thousands of patients treated for a variety of diseases attests to its safety and relative lack of morbidity. Patients are regularly monitored during the procedure by physicians and nurses. In a report describing 153 apheresis treatments, the morbidity was minor (nausea 5 percent, vomiting 3 percent, paresthesia 7 percent, allergic hives 3 percent, transient hypotenison 11 percent) and no procedures were terminated because of these reactions (50).

Mortality associated with apheresis has been estimated to be at a rate approximately 3 per 10,000 procedures. Of the 42 reported deaths associated with apheresis, 60 percent were cardiovascular (arrhythmia or arrest) or respiratory (pulmonary edema or respiratory distress syndrome) (52). Other rare events included anaphylactic reactions, sepsis, hepatitis, pulmonary embolism, hemorrhage and coagulation abnormalities (53,54).

DISCUSSION

The rational treatment of a disease should ideally derive from an understanding of its pathophysiology. In the case of SLE, its pathophysiology has not been definitively elucidated despite considerable evidence supporting autoimmune mechanisms effecting the clinical manifestations in a majority of SLE patients (27). The variable natural history of SLE includes fluctuations in clinical status and occasional dramatic spontaneous improvement.

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The efficacy of apheresis in the treatment of SLE has been attributed to the physical removal and/or dilution of CIC and antibodies plus an improvement of RES function in CIC clearance. However, the mechanism of action of apheresis is non-specific and remains hypothetical. The benefit of apheresis has been claimed for some patients without evidence of high levels of CIC (37). Apheresis should properly be performed in cases where there is a demonstrable circulating factor responsible for the disease. Although specific plasma constituents have been isolated in some SLE patients these have not always been correlated with disease activity. It is possible that some of the plasma factors seen in SLE patients may be a consequence of the disease rather than its cause.

No controlled clinical trial has yet demonstated that apheresis is of benefit in SLE despite many reports of marked but short-term clinical improvement.

The NIH is currently supporting a 5 year multi institutional study to determine short and long term efficiency of apheresis in 125 patients with SLE nephritis. The study is expected to be completed in 1988-89. A decision is expected to be made in March, 1986 on whether sufficient patient accrual and data is available to terminate the study.

In addition to the question of efficacy of apheresis in SLE, unresolved issues include; the frequency of treatment, the optimal amount of plasma to be exchanged and the nature of the replacement fluids.

A recent review of the literature, that included 130 patients with SLE who were treated with apheresis, indicated a "significant remission" in approximately 60 percent of cases (35). The mix of cases and the time of associated treatment is left unspecified, so that the exact role of apheresis is not clear.

Schlansky et al. introduced a note of caution in the treatment of SLE using apheresis without concomitant immunosuppression or steroids (41). In 4 patients in whom apheresis was the sole therapy, the well-being reported by the patients following apheresis was associated with exacerbation of clinical and laboratory parameter in all 4

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patients during the 6 months of followup.

The reasons for the failure of apheresis to effect clinical improvement in all patients is not known, but may be related to the absence of specific circulating immune factors in the individual patient.

The University of Kansas Medical Center Immunology Lupus Service has informed OHTA that they recommended apheresis be employed for patients with active disease who have failed to respond to conventional immunosuppression.

The American Academy of Dermatology has informed OHTA that although the long-term value of apheresis in the treatment of SLE is not clear, it may be valuable as adjunctive therapy for the seriously ill patient who shows evidence of CIC and is not responsive to standard medical treatment.

The AMA Council of Scientific Affairs, Division of Drugs and Technology has included SLE in their list of diseases for which the available evidence "tends to favor" efficacy for apheresis (1).

The American Society for Apheresis has informed OHTA that the summary of clinical evidence suggests benefit of apheresis in patients with serious active SLE, including CNS disease or rapidly progressive nephritis.

The NIH has informed OHTA, in June, 1985, that the efficacy of apheresis in the treatment of SLE is still unproven. They have recommended that the use of apheresis for the treatment of SLE be reserved for the treatment of patients with acute or severe disease who have failed to respond to other therapies and be preferably done under investigational protocols to help resolve questions regarding its use in specific patient populations.

The Food and Drug Administration has stated that the commercially available centrifugal cell separators used in apheresis procedures were developed prior to the enactment of the Medical Device Amendments and were not within the realm of their review.

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The membrane-type apheresis devices were not commercially available prior to the enactment of the Medical Device Amendments. By statute, the membrane devices are classified into class III and require a premarket approval application (PMA) to be filed with FDA before the device is made commercially available. To date, six PMA applications which include the filters for therapeutic apheresis, have been approved by the FDA. The six membrane-type separators are approved as safe and effective for use in plasma separation.

The equipment which controls the blood pressure and flow rate during the therapeutic procedure has been found to be substantially equivalent to class II medical devices. To date, four 510(k) applications have been reviewed by FDA for the equipment used with apheresis membranes for therapeutic apheresis.

A Federal Register notice of this assessment was published on April 3, 1985 (55).

SUMMARY

The view that SLE is an immune-complex disease, makes treatment by apheresis attractive via the mechanisms of physically removing antibody, antigen, CIC and mediators of inflammation and/or facilitating their endogenous clearance. The relative safety of apheresis has been well documented.

Despite 10 years of widespread clinical experience in Europe and North America, the efficacy of apheresis in the treatment of SLE is still unproven.

Data from a large and growing number of case reports and series have suggested that apheresis is a useful adjunct to conventional therapy for the treatment of SLE. However, this has not been established in any controlled clinical trial.

A large ongoing NIH supported clinical trial of apheresis in the treatment of severe SLE nephritis is designed to resolve many of the questions regarding apheresis in this specific patient population.

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Until such time as data from randomized controlled clinical trials prove the efficacy of apheresis in the treatment of SLE it is recommended that its routine use be reserved as an adjunct to conventional therapy for patients with life threatening disease in whom steroids and other immunosuppressive drugs have failed to prevent clinical deterioration.

Prepared by: Harry Handelsman, D.O.

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Harry Handelsman, D.O.

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Office of Health Technology Assessment
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12. Sponsoring Organization Name and Address
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In-house

14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Apheresis is a procedure which employs a blood processing machine to selectively remove plasma or other blood components from the circulation. It is most often used to collect donor platelets or leucocytes, but has been successful in the treatment of some autoimmune diseases. Apheresis has been investigated in the treatment of a number of diseases presumed to be immunologically mediated. Although the pathogenic mechanisms of systemic lupus erythematosus are not completely understood, there is considerable evidence implicating circulating factors in the generation of tissue injury. Theoretically, removal or dilution of circulating immunopathogens may favorably affect the course of the disease. Data from a large and growing number of case reports and series have suggested that apheresis is a useful adjunct to conventional therapy for the treatment of systemic lupus erythematosus. However, until such time as data from randomized clinical trials prove the efficacy of apheresis in this disease, its use should be reserved for those patients with life-threatening disease in whom conventional therapy has failed to prevent clinical deterioration.

17. Document Analysis a. Descriptors
NCHSR publication of research findings does not necessarily represent approval or official endorsement by the National Center for Health Services Research and Health Care Technology Assessment or the U.S. Department of Health and Human Services.

b. Identifiers/Open-Ended Terms
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